'PRONTOSIL'

A Survey of the
New Chemotherapy

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FOREWORD

It is not necessary here to enlarge upon the importance of the contribution which Prontosil has made towards the treatment of disease. Since its introduction in Germany, in 1935, *it has aroused the greatest interest throughout the world. The abundance of publications in the medical literature, however, makes it difficult for doctors to get a clear idea of the most important experimental and clinical facts that are now known about these drugs.*

In this booklet an attempt has been made to collect and classify these facts so that information on any particular question can be rapidly obtained. Only two hundred of the more important references (about one-fifth of the total available) have been chosen, and these give chapter and verse for all the statements made. The contents are arranged in three main sections—Experimental Findings, Clinical Experience, and Therapeutics—and are, we believe, more in the nature of a well-balanced review of the subject than a collection of summaries of published work.

One word should be added on the matter of terminology. The three available preparations, Prontosil Rubrum, Prontosil Soluble, and Prontosil Album are briefly described on p. 6 *(immediately following the list of contents). To avoid confusion it may be stated here that Prontosil Album (p-amino-phenyl-sulphonamide) is the Bayer brand of sulphanilamide, a term used in the English and American literature.*

MEDICAL DEPARTMENT,

BAYER PRODUCTS LTD.

May, 1938.

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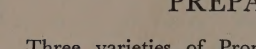
NATURE OF 'PRONTOSIL'* PREPARATIONS

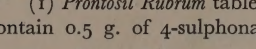
Three varieties of Prontosil are marketed, (1) Prontosil Rubrum (syn. Prontosil Red), (2) Prontosil Soluble, and (3) Prontosil Album.

(1) *Prontosil Rubrum* tablets, intended for oral administration, contain 0.5 g. of 4-sulphonamide-2', 4'-diamino-azo-benzol :



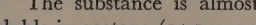
The substance is almost insoluble in water, but is easily soluble in acetone (14.1 per cent.), moderately soluble in alcohol (0.55 per cent. in 90 per cent. and 0.38 per cent. in absolute alcohol), and soluble to about 9 per cent. in a mixture of 95 per cent. alcohol and acetone in equal parts (the figures given are for solution at 20° C.). The addition of dilute HCl forms the hydrochloride, which has a melting point of 248°-250° and dissolves with difficulty in cold but easily in hot water.

(2) *Prontosil Soluble,* which is given by injection and prepared in ampoules containing 5 c.c. of a 2.5 per cent. or 5 per cent. solution, consists of the di-sodium salt of 4'-sulphonamido-phenyl-azo-7-acetylamino-1-oxynaphthaline-3, 6-disulphonic acid:



In a dry state the compound is soluble in absolute alcohol, ether, acetone, chloroform, and benzol.

(3) *Prontosil Album,* which is supplied in 0.5 g. tablets for oral administration, consists of the colourless para-amino-phenyl-sulphonamide :



The melting point of this substance is 165–166° C. and it is soluble in acetone and dilute hydrochloric acid. The solubility in cold water is 0.5–0.8 per cent., but it is much more soluble in boiling water.

* 'Prontosil,' brand of puerperin, is a registered trade mark.

EXPERIMENTAL FINDINGS

EXPERIMENTAL FINDINGS

Chapter I.

PHARMACOLOGY

The most remarkable fact about the Prontosil group of drugs—especially when it is contrasted with their therapeutic potency—is their pharmacological inactivity, which has been demonstrated by several experiments. Thus, Weese and Hecht (1935), using Prontosil Rubrum, could perceive no change in the blood pressure or the action of the heart after the rapid intravenous injection of 10 mg./kilo in animals, and the smooth muscle of the uterus and intestine did not respond to the drug in investigations carried out on isolated organs or the living animal. Hawking (1937), using Prontosil Album (actually sulphanilamide), noted no pharmacological action on rabbit intestine, guinea-pig uterus, or frog heart, while in cats and dogs given 0.7 g./kilo intravenously no rise in blood pressure was obtained.

Details of Tolerance

The drugs are well tolerated by animals. Domagk (1935) stated that rabbits and mice tolerated 0.5 g./kilo by mouth and subcutaneously (Prontosil Rubrum); rabbits receiving 0.1—0.2 g. orally for 14 days showed no ill-effects, the urine and blood picture remaining normal. Hörlein (1935) also stated with regard to Prontosil Soluble that mice tolerated 1 c.c. of 4 per cent. solution intravenously and 2 c.c. intramuscularly, while rabbits tolerated 0.1—0.2 g./kilo intravenously. When higher doses were used, as by Hawking, who gave sulphanilamide 1.5—2 g./kilo to rabbits, weakness of legs, dyspnœa and a rigid extension of limbs and contraction of head resembling decerebrate rigidity developed: some of these animals recovered and on examination no changes were found in the liver, kidneys, and viscera. In three animals degenerative changes were observed in the anterior spinal column cells, and some cells of the cortex, but the author pointed out that the effects followed doses which would not be used in practice on human beings.

Marshall et alii (1937) also investigated the toxicity of sulphanilamide, giving the drug in 10 per cent. suspension in

acacia. They found the lethal dose for 50 per cent. of the mice to be 3.8 g./kilo, while for 100 per cent. it was over 10 g./kilo. Doses of 0.1—0.2 g./kilo given to dogs produced no symptoms, but when 0.5—0.6 g./kilo was given various symptoms developed and one dog died. These symptoms included salivation, vomiting, diarrhoea, muscular weakness, excitement, ataxia, and in some cases rigidity of the limbs. Neither toxic effects nor pathological changes were observed in dogs and rabbits who were given sulphanilamide for some months, and, although a temporary decrease in renal function was noticed after a large dose, no permanent renal injury could be detected. In addition, no consistent changes in the cell count, or in the differential count, could be demonstrated after large doses of the drug.

It may be of interest here, by way of summary, to record the results of experiments in the Elberfeld Laboratories on different animals :

" On account of the low toxicity of Prontosil, it was difficult to arrive at the lethal dose because of the large quantities of the drug and the large volumes of fluid which had to be used. Thus, rats tolerated 3 g./kilo. of Prontosil Rubrum or Prontosil Album without upset. In mice, although 2 g./kilo. of Prontosil Rubrum constituted the border-line lethal dose, a similar amount of Prontosil Album was tolerated. In cats 1 g./kilo. of the former was vomited without further disturbance, while a similar dosage of Prontosil Album was found to be the minimum lethal dose. This was in contrast to the guinea-pig, in which the border-line dosage of Prontosil Album was 2.5 g./kilo., while for Prontosil Rubrum the border-line was 1 g./kilo. In dogs 1 g./kilo. of Prontosil Album was barely fatal, and these animals showed an unusual sensitivity to Prontosil Rubrum. Prontosil Soluble was completely harmless in oral doses of 3 g./kilo. in mice and guinea-pigs.

" Using Prontosil Soluble given by injection the following doses were arrived at. The mouse just tolerated 1.25 g./kilo. given intravenously. In cats and guinea-pigs the intramuscular injection of 3 g./kilo. caused an intense staining of the whole body but no marked toxic effects. The cats vomited and the guinea-pigs remained quite active ; in both species slight and irregular variations of temperature, above and below the normal level, were noted. Dogs tolerated 2 g./kilo. intramuscularly without injury.

" In general the symptoms of poisoning with large doses of Prontosil Rubrum and Prontosil Album in cats and dogs were those of central stimulation along with some degree of paralysis ; these symptoms, which did not appear when vomiting was caused, were seen after several hours, and in the cases of border-line doses sometimes ended in death after 24 hours. In some cases after the highest doses diarrhoea appeared.

" Although the Prontosil compounds appear to possess a very low toxicity when administered on a single occasion in animal experiments, the possibility of cumulative poisoning, the mechanism of which is not yet clear, must not be overlooked. None the less, in several instances in which dogs were given 0.1 g./kilo. Prontosil Rubrum or Prontosil Album by mouth and 0.1 g./kilo. Prontosil Soluble intravenously for several weeks, no toxic effects were seen ; the body-weight, the urine and the blood picture remained unaffected."

It may be concluded, from the investigations so far reported, that the drugs are on the whole well tolerated by tissues and organs.

Effect on Hæmopoietic Tissues

In view of the occurrence of cases of agranulocytosis, however, the behaviour of the hæmopoietic system is of particular importance ; and, as the animals appear to be unaffected in this respect, the results of human investigations must be considered. Osgood (1938) noted that a concentration of 1 : 1000 sulphanilamide had no effect on cultures of human bone-marrow cells over a period of eight days. Bigler et alii (1938) investigated the leucocyte response to sulphanilamide in 33 patients, some with leucocytosis from infection, and others with normal blood counts. Because of the fact that the leucocyte count increased during the administration of sulphanilamide in only three instances, that the leucocytes fell with unusual rapidity on recovery in other cases, and that leucopenia developed in two cases, the authors felt that sulphanilamide caused a depression of the leucocytes ; this was not accompanied by agranulocytosis, however, as no relative reduction in the various elements occurred. The hæmoglobin percentage and the red blood corpuscles appeared unaffected. In the series of ten cases reported by Campbell (1938) no change in the leucocytes, red cells, or hæmoglobin was observed ; and he concluded, because of a rise in the reticulocyte level in some cases, that moderate doses of sulphanilamide seemed to act as a mild stimulus to the bone-marrow.

Blood Pigmentation

Bigler et alii, in addition to the findings mentioned above, noticed that in some patients who developed cyanosis a pigment was obviously present in the blood, although no spectroscopic changes could be detected. The nature of this pigment has not yet been determined, but Rimington (1938), studying the porphyrin excretion in patients and animals receiving sulphanilamide, elucidated new facts on the effect of the drug on pigment formation. One point of interest, which tended to contradict Marshall and his co-workers' findings on excretion of sulphanilamide, is that rats continued to excrete sulphanilamide for 21 days after cessation of prolonged dosage. It was also shown that the urines of rats and patients, in almost all cases, contained abnormally large amounts of porphyrin, which persisted for some time after discontinuance of the drug. The isolated porphyrins were coproporphyrin I, which arises from some derangement of the hæmopoietic system and which is most

active as a photosensitizer, and coproporphyrin III, which is associated with impairment of hepatic efficiency.

In animals the spleens were found to be blackish-brown and engorged, and deposits of a greenish-brown granular pigment and much stainable iron were found. The author suggested that sulphanilamide might cause some degree of blood destruction, and raised the suspicion of a deep-seated action on the hæmopoietic system. This work, while of great scientific interest, has not yet been related to the toxic effects of the drugs, although it might be shown that the coproporphyrin I formation is related to the allergic or light-sensitive rashes.

Chapter II.

ABSORPTION AND EXCRETION OF PRONTOSIL

Since the three varieties of Prontosil behave somewhat differently on ingestion, they will be considered separately.

Prontosil Album

The fullest investigation into the absorption and excretion of Prontosil Album (sulphanilamide was actually used) was made by Marshall and his co-workers (1937). It was shown that the absorption of the drug after oral administration was very rapid, being complete or nearly so in four hours. In dogs, parenteral administration did not cause a higher level of the drug in the blood than oral administration. It appeared, moreover, that this compound spread to all parts of the body, as it was recovered from the saliva, pancreatic juice, bile, pleural fluid and cerebro-spinal fluid; in the dog the cerebro-spinal fluid level was slightly lower than that of the blood.

Although Fuller (1937) suggested that sulphanilamide was not completely excreted, some being destroyed in the body, the above workers concluded that, after equilibrium had been established by two or three days' regular dosage, about 100 per cent. of the drug could be recovered from the urine. In the dog the drug was excreted unchanged, whereas in man and rabbits it was excreted partly unchanged and partly converted into an acetylated form. The authors also concluded that a concentration of the drug of from 1:5000 to 1:10,000 in the blood could be attained and kept by regular and sufficiently large four-hourly doses. It is of clinical interest to note that in the presence of impaired renal function a smaller dosage was sufficient to achieve the desired level.

Prontosil Soluble

This compound is absorbed with great rapidity, as is shown by the discoloration of the urine which appears within ten minutes of the injection. Following a suggestion by Nitti and others (1936), Fuller showed that the Prontosil Soluble was partly converted into sulphanilamide (i.e., Prontosil Album), which appeared in the urine 4—6 hours after the first dose; again, the sulphanilamide was partly free and partly acetylated. Jauerneck and Gueffroy (1937) and Millett (1937) also showed

that Prontosil Soluble appeared in the cerebro-spinal fluid, as did some Prontosil Album derived from the coloured drug. In the healthy subject, according to Jauerneck and Gueffroy, the cerebro-spinal fluid level of Prontosil Soluble was only 1/200th of the blood level, but in the presence of inflammatory meningeal disease (e.g., meningitis) it was found that Prontosil Soluble passed freely into the cerebro-spinal fluid.

Fuller (1937) stated that a moderate dose of Prontosil Soluble was excreted by the mouse in about six hours, and Rosenthal et alii (1937), working with rabbits, recovered 85—95 per cent. of the compound in the urine five hours after intramuscular and intravenous injection; the proportion of sulphanilamide recovered was not stated. In addition, 4—8 per cent. was recovered within two hours from the bile of rabbits. It is obvious, from the findings, that Prontosil Soluble is rapidly excreted.

Prontosil Rubrum

This compound, although it appears in the urine within an hour of oral administration, differs markedly from the other two as regards excretion. Like Prontosil Soluble it is partly broken down to sulphanilamide in the body, as was shown by Fuller (1937); but this author also reported that only a small fraction of a dose of Prontosil Rubrum, given in a 10 per cent. gum suspension, by mouth to a mouse, was excreted in five days. A similar fact was previously noted by Colebrook, Kenny and others (1936), who found that a subcutaneous injection of 10 per cent. Prontosil Rubrum in aqueous suspension protected the mouse from infection with streptococci four days later. Neither Prontosil Album nor Prontosil Soluble had this protective property, and the mice continued to excrete Prontosil during the 26 days of life after receiving the drug. On killing the animals a large deposit of undissolved Prontosil was found at the site of injection.

Whether these observations have any bearing on the treatment of human beings cannot be determined from the literature available, but it is plain that such a "delayed action" on the part of Prontosil Red would be valuable in certain circumstances.

Chapter III.

MODE OF ACTION

The problem of the action of Prontosil has been attacked with zest by several investigators, but so far no one has been able to explain the discrepancies which have arisen. The work done, however, has produced certain negative conclusions, and has demonstrated how fascinating and difficult the whole subject is. Two questions arise : one is the nature of the substances possessing or producing the active principle of the chemotherapeutic effect, the other is the action of this principle.

The Active Principle

The fact that Prontosil Soluble and Prontosil Rubrum give rise to Prontosil Album in the body has already been mentioned, and shortly after this fact was established a tendency to explain the action of all three drugs on this basis arose, as it was assumed that the coloured compounds were of value only by virtue of the sulphanilamide produced. This hypothesis, however, cannot be regarded as proven, since it fails to reconcile several points. In the first place, all three Prontosils, while partly excreted (in man) as sulphanilamide, are also partly excreted as an acetylated compound which, according to Domagk (1937) has a low chemotherapeutic activity. The significance of this compound has never been settled. Moreover, Domagk (1937) has described active chemotherapeutic compounds which do not yield sulphanilamide, but appear to be excreted unchanged ; and Buttle et alii (1937), who showed that a compound called 4-diaminodimethylsulphone had a high degree of activity in infected animals, considered it highly improbable that this drug was reduced to sulphanilamide in the body.

Another fact of interest is that the coloured drugs, even if completely reduced in the body, yield a much smaller amount of sulphanilamide than would be obtained by giving an equal weight of sulphanilamide alone. That being so, the coloured drugs should be much less active, weight for weight, than sulphanilamide, a fact which is not borne out by clinical experience in which the azo-compounds and sulphanilamide, in roughly similar dosage, gave at least equally good results.

Rosenthal et alii (1937), however, stated, as a result of

experiments on rats and mice infected with streptococci and meningococci, that Prontosil Rubrum and Prontosil Soluble were less effective than sulphanilamide. The same workers also concluded that the rapidity of excretion of Prontosil Soluble after injection was so great as to leave a surprisingly small amount to be activated by reduction, and from this suggested that the intact molecule might possess therapeutic activity. These discrepancies are increased by Domagk's report that injections of Prontosil Soluble given to infected mice at 24-hourly intervals (the treatment beginning one hour after infection), prevented a fatal spread such as occurred in the controls. In this connection another observation of Domagk's is of interest: on comparing the peritoneal smears of mice infected for four hours with streptococci and treated with Prontosil Soluble, as against controls, he found the microscopic picture almost normal, whereas in the infected mice the smear showed numerous cells and cocci. If the activity of Prontosil Soluble depended on the sulphanilamide derived from it, one would not, in view of the rapidity of the excretion of the drug in a largely unchanged form, expect such therapeutic activity.

Levaditi (1937) also supported the view that the coloured drugs did not depend for their activity on reduction to sulphanilamide. He stated that, according to Levaditi's and Vaisman's work (1937), and that of others, the azo-compounds were more powerful therapeutically than sulphanilamide; and mentioned that an azo-compound synthesised by Gley and Girard (1936), which yielded the same amount of sulphanilamide as a related azo-compound, was yet more powerful in action than the second drug. This tended to show that the activity of the coloured drugs was *not* proportional to their sulphanilamide content, as would be expected if their activity arose solely from reduction to the latter drug.

Bacteriostatic Experiments

Despite the above considerations, which would appear to indicate that the presence of sulphanilamide either alone or as a constituent of another drug is not essential for chemotherapeutic activity (since active drugs which neither contain nor produce sulphanilamide are known), experiments on the action of various Prontosils in vitro have been cited as evidence that their activity is due to their sulphanilamide content. It is admitted that the coloured drugs have no bactericidal or bacteriostatic effect in vitro, but several workers have claimed that sulphanilamide possesses the power of killing bacteria outside the body. Thus Colebrook, Buttle et alii (1936) found that a 1 : 10,000 concentration of sulphanilamide in ordinary culture media could delay

the growth of 30—50 cocci for 2—5 days, but that in human blood a concentration of 1 : 30,000 could destroy an inoculum of 3,500 cocci per 5 c.mm. The results in animal blood were not nearly so striking.

Hoare's findings (1938) indicated that whole blood containing sulphanilamide had a marked bactericidal action in low concentration, 1 : 60,000 to 1 : 16,000, while serum containing sulphanilamide was comparatively inactive above 1 : 16,000; and Osgood (1938) reported that cultures of hæmolytic streptococci in living bone-marrow cells were sterilised by the addition of a concentration of sulphanilamide up to 1 : 100,000. Domagk (1937), however, could detect no significant effect in vitro, as some strains which were not vulnerable to sulphanilamide outside the body responded to treatment in the infected animal as well as other strains which were vulnerable in vitro. Long and Bliss (1937), too, failed to confirm Colebrook's and his co-workers' findings concerning the bactericidal property of serum from patients receiving sulphanilamide.

Bürgers (1938) was also unable to show that Prontosil Soluble or Prontosil Album produced a bactericidal effect in the blood or test-tube, and he formed the opinion that the activity of the azo-compounds did not depend on their liberation of sulphanilamide.

It was suggested that Domagk's and Long and Bliss's failures to detect a bactericidal effect could be explained by the use of too large inocula (Hoare 1938), and by the fact that the effects were more easily obtained in culture with a limited air supply (Colebrook 1937). Rosenthal (1937) reported that no bactericidal effect could be obtained from sulphanilamide in broth culture against streptococci, staphylococci or *B. coli*, but that pneumococci of Types I, II, and III were destroyed by low concentration of sulphanilamide in broth culture; while Kenny et alii (1937) reported a marked bactericidal effect, which did not, however, correspond in all cases to the effect produced in infected patients, against *B. coli* in concentrations varying from 1 : 1000 to 1 : 4000.

It must be admitted that sulphanilamide has been shown by certain workers to possess bactericidal effects against certain organisms in vitro. Apart from Rosenthal's findings with pneumococci, however, the effects, when concentrations obtainable in the body are considered, have all been achieved in the presence of cells or serum, or both, and only when these cells and serum were human in origin. This tends to show that the action of sulphanilamide and the other drugs cannot be a simple disinfectant or bactericidal action, but that it is related in some way with the activities of the body.

It has been shown that the nature of the active principle is undecided ; and another possibility is that the various compounds have the power of producing a single substance, capable of isolation and preparation, in the body. Levaditi (1937) put forward such a hypothesis, and suggested that this substance was produced in the reticulo-endothelial system, and that the azo-dye played an important part in concentrating the drug in that system. Domagk (1937), who did not, however, postulate an X-substance, suggested that Prontosil Rubrum might be reduced in the reticulo-endothelial system, in much the same way as gold-compounds ; but he admitted the difficulty of thus explaining the action of the non-reducible drugs. Were the X-substance shown to exist it might prove to be intensely lethal to bacteria, thus rendering the bodily defences unnecessary. The other possibility is that several drugs have the peculiar property, not of producing one uniform anti-streptococcal agent but of assisting the bodily defences, in an undetermined manner, to overcome the infection.

Several observers believe that these drugs exert an action sufficient to enable the phagocytes to deal with the organisms ; this was put forward by Long and Bliss (1937a), who examined hourly peritoneal smears from mice infected with streptococci and given sulphanilamide. For 6—15 hours the organisms multiplied, then suddenly a wave of phagocytes appeared and the organisms were ingested. During this period of multiplication the organisms retained their capsules and were virulent to other animals. Domagk (1937), on the other hand, found that the peritoneal cavity in infected mice treated with Prontosil appeared almost normal in a few hours, and Mellon and others (1937) found little evidence of phagocytosis in smears from peritoneal exudate and sections of liver and spleen in infected mice treated with sulphanilamide. Another theory put forward by Levaditi (1937), Osgood (1938) and others was that Prontosil neutralised the toxins produced by streptococci. This suggestion awaits further investigation.

To summarise, no decision on the action of Prontosil is at present possible : whether the drugs act by affecting the organisms more than the body is an open question, but it is highly probable that in some way the process is a vital one which will not be explained in terms of the chemical actions of these preparations.

CLINICAL EXPERIENCES

CLINICAL EXPERIENCES

Chapter IV.

GENERAL INFECTIONS

1. Puerperal Sepsis

Puerperal sepsis is not a disease with special characteristics and symptoms, but rather a condition resulting from the entry of organisms into the body during or after childbirth by a route not normally available, the female genital tract. Many of the subsequent manifestations may occur in non-parous individuals. Although the invading organism is most commonly a hæmolytic streptococcus, other organisms may in rare cases be responsible. The effects produced are variable, ranging from mild local infection to generalised peritonitis and septicæmia, and the prognosis varies with the severity of the infection. It is obvious, therefore, that the assessment of any treatment for this condition is a matter of difficulty.

Cases on Coloured Prontosils

The first clinical trials of Prontosil in puerperal sepsis in England were carried out by Colebrook, Kenny, and the staff of Queen Charlotte's Hospital (1936a and b). In all, 64 cases were treated, Prontosil Rubrum and Prontosil Soluble being given together in most instances. The total daily dosage varied from 2—5.5 g. at the commencement of treatment, and the amount given was reduced 1 or 2 days after the temperature fell. In almost all cases the infecting organism was the *Streptococcus hæmolyticus*, Group A (Lancefield), and the severity of the illness varied greatly. The results of this investigation were analysed with great care, the fluctuating nature of the condition and the possibility of a diminution in virulence of the organism being kept in mind.

It was concluded that in 28 cases of mild infection, recovery would have occurred without Prontonsil treatment, but that in 36 cases Prontosil had played a part in bringing about recovery. There was a "sudden and remarkable fall in the death-rate for all cases admitted with an infection by the hæmolytic streptococcus," a fall which could not be accounted for entirely

without admitting the influence of Prontosil : 7 out of 8 cases of peritonitis (1 patient having a positive blood culture) recovered, while of 8 patients without peritonitis in whom a positive blood culture was obtained 6 recovered. Another point of interest was that in the cases treated with Prontosil no palpable pelvic inflammatory masses could be detected, whereas in 4 out of 20 patients in whom the condition had been considered too mild for Prontosil treatment a spread of infection occurred resulting in irregular fluctuations of temperature and the appearance of masses in the pelvis. In the great majority of Prontosil-treated cases the temperature fell within 24 hours and remained normal, and in no instance did the patient have to be kept in hospital for several weeks while the pelvic inflammation resolved. In considering isolated cases, such as that of a patient who recovered after developing a septicæmia of the type hitherto associated with a terminal infection, astonishing recoveries were noted.

Cases on Prontosil Album Alone

The next publication on this subject was that of Foulis and Barr (1937), who used Prontosil Album in doses of 3—14.4 g. daily, continuously, until the temperature fell, and thereafter for a few days ; four of the patients had in addition occasional doses of Prontosil Soluble. In all, 22 cases were treated ; of 11 with septicæmia a positive blood culture for the hæmolytic streptococcus was obtained in 8, and a hæmolytic streptococcus was also cultured from the peritoneal fluid of 3 cases of peritonitis without septicæmia. The remaining 7 patients were shown to have hæmolytic streptococci in the vaginal discharge. The results in this group were striking. One patient died giving a mortality rate of 1.4 per cent. for the whole series, as compared with an average of 17.4 per cent. for a 5-year period in the same hospital. In the recovered cases the fall in temperature and the general improvement were rapid. In spite of the large doses the only toxic symptoms were slight cyanosis in 2 cases, mild albuminuria in 2 cases and sickness and vomiting in 1 case. It cannot be admitted that this experience accords with that of other observers.

Another Group on Oral Treatment

A further series of 106 cases of puerperal fever treated with sulphanilamide was reported by Colebrook and Purdie and the Honorary Staff of Queen Charlotte's Hospital (1937a and b). Of 100 cases the infecting organism was the hæmolytic streptococcus (Lancefield) in 92 ; 3 patients were infected with non-hæmolytic streptococci, and 3 with staphylococci. The clinical course of the cases of hæmolytic streptococcal infection was on the whole similar to that of the series mentioned above, except

that resolution of the infective process seemed a little less spectacular, and the average stay in hospital was 19.7 days as compared with 31.3 days in 1935. Although the death-rate was 8 per cent. as against 4.7 per cent. in the previous series, only 3 deaths could be regarded as due to straightforward sepsis, for the remaining patients died from hæmorrhage, pulmonary embolism and perforation, or did not live long enough to receive a sufficient amount of sulphanilamide.

Analysis of Results and Dosage

In the above paper the important question of the diminished virulence of the organism was also discussed, and, as it had been suggested by Gibberd (1937) that the streptococcus had recently assumed a less " invasive " character, an attempt to define the mortality-rate in " invasive " cases alone was made. The death-rate for such cases was found to be 27.3 per cent. under treatment with Prontosil and sulphanilamide, as against an average of 71 per cent. for the previous 4 years. This suggested to the authors that the case mortality had been reduced more by the treatment employed than by lack of " invasiveness " on the part of the streptococci.

In considering dosage the authors did not feel that the large amounts employed by Foulis and Barr (1937) were necessary in infections of average severity, but they recommended doses of from 8—15 g. daily for a few days in extremely severe infections. It is interesting to note that no correlation between the increase in dosage and the incidence of toxic effects could be determined.

2. Prophylaxis of Puerperal Sepsis

It is now generally agreed that Prontosil is of great value in the treatment of puerperal sepsis, but whether or not it is justifiable to use the drugs prophylactically in normal cases is a debatable point. Those who object to this course argue that no evidence of protective value is available, that certain by-effects from the preparations are to be feared, and that the extent of the risk of infection with virulent organisms during normal confinements is not known. Moreover, many observers consider that the widespread use of this measure, even if it were shown to confer protection, would bring about an undesirable relaxation in aseptic and antiseptic technique. It cannot be denied, however, that unexpected and fatal infections may arise in confinements conducted with reasonable care and cleanliness. This is illustrated in the tragic case recorded by Colebrook (1936) in which the death, from septicæmia, of an otherwise healthy young woman was attributed to infection conveyed by a nurse who had come from a case of tonsillitis in a children's hospital.

Experimental evidence tends to show that injections of Prontosil can protect animals against high doses of virulent organisms given a few hours later. The first clinical observations were recorded by Ley (1936), who used Prontosil by injection, orally, and rectally, in 42 cases in which fever following operation would normally have been expected.

French Experience

Lacomme (1937) next reported the results of prophylactic treatment in 3,089 patients, using as a comparison the morbidity and mortality rate in 26,000 patients confined in the Baudelocque Clinic from 1926 to 1934. He used two coloured preparations closely related to Prontosil Rubrum. Treatment was begun on the patient's entry into the labour ward with 2 g. of the "chlorhydrate" compound or 1.6 g. of the "carboxy" compound daily, administration being continued for 4 or 5 days after delivery. The results showed that puerperal infections had been definitely less numerous and notably less severe during 1936, the year of the trial, than during the most favourable preceding year. The number of cases treated prophylactically was thought too small for definite conclusions, but if the causes of the improved statistics were considered to be fortuitous coincidences, the author claimed the right to be surprised at the number and variety of these coincidences. He also stated that it did not seem fanciful to count on a considerable diminution in moderately severe infection and, above all, in the sudden and unexpected septicæmic infections which occurred in normal delivery and often led to death. In considering the marked increase in the number of cases of phlebitis, it was suggested that the prophylactic treatment might have been responsible for this by bringing about diminution in the virulence of the organism.

English Experience

Another extensive investigation was carried out by Williams (1937), who used Prontosil Album prophylactically in 140 cases, 162 being left untreated as controls. The drug was given in the third stage of labour, in most instances shortly after delivery, and doses consisted of 2.7 g. daily continued for a week; 4-hourly temperature charts were kept. Analysis of the results disclosed little difference in the morbidity rate in the two series, but the only four cases of severe infection occurred in the controls; two of these were septicæmia due to *Staphylococcus aureus* and *B. coli* respectively, one had pelvic peritonitis, and in another a sterile peritonitis of obscure origin occurred. It is interesting to note that hæmolytic streptococci were cultured from vaginal swabs in seven of the control cases, whereas in the

Prontosil-treated cases no positive cultures were obtained in a much larger number of examinations. A large scale experiment was also made by Johnstone (1937) using Prontosil Album and *p*-benzylaminobenzene sulphonamide in two different groups of patients. The combined figures showed a fall in the incidence of local uterine infection and in puerperal morbidity (B.M.A. Standard). There was little evidence of any toxic effects and apparently little to choose between the two drugs.

Conclusions as to Value

It may be stated that, at the moment, no definite conclusion on the value of prophylactic Prontosil treatment in normal cases is possible, and any conclusion as to whether or not such a treatment is justifiable depends upon whether the risk of infection in normal confinements is greater or less than the risk of serious toxic effects from the drugs. There can be no question, however, of the advisability of using Prontosil in all cases in which the possibility of a serious infection exists. Such a possibility arises when the patient or any one in her immediate surroundings suffers from, or has recently recovered from, tonsillitis, scarlet fever, antrum infection, otitis media and discharging wounds. It is probable that prophylactic treatment is also advisable in cases in which operative interference has occurred during delivery. Any patient who exhibits a rise of temperature during the puerperium should be given Prontosil immediately, without awaiting the results of bacteriological investigation. Thereafter the treatment may be suspended or continued as indicated.

3. Septicæmia

In addition to the papers referred to in the first part of this chapter a large number of reports on the use of Prontosil in severe streptococcal infections has been published. Thus, Imhäuser (1935) treated 11 patients with symptoms of septicæmia successfully, and Schranz (1935),who treated 66 patients suffering from septicæmia with Prontosil, noticed particularly favourable results in puerperal fever and infected abortion.

4. Erysipelas

As the mortality-rate from this disease is low it is essential, in assessing the value of any method of treatment, to note how the symptoms are affected, and most workers have estimated the efficacy of Prontosil by its effect on the duration of spread of the rash, the duration of pyrexia, and the patient's general condition.

Results

Snodgrass and Anderson (1937a) demonstrated in a series of carefully controlled cases treated with Prontosil Rubrum and Prontosil Soluble that " those cases which received Prontosil showed better results in respect of curtailment of the above factors " ; while in a second paper (1937b) these workers, using sulphanilamide, confirmed the previous findings. It was also noted that the drugs reduced the incidence of complications and diminished the tendency to recurrence—facts of importance considering the comparative frequency of these features of erysipelas. Other observers include Becker (1937), Kramer (1936), Tonndorf (1936), and Minkenof (1936) ; one of the latter's patients, who suffered from relapsing erysipelas for a year with occasional afebrile periods of one week's duration, remained free from attack for months after Prontosil treatment.

In the majority of cases reported the rash ceased to spread within 24 or 48 hours, the temperature was normal by the fourth day, and the general condition was greatly improved by the fifth day. The average duration of stay in hospital, as compared with control cases, was also reduced.

Dosage

This varied from 2—6 g. of Prontosil Rubrum or Prontosil Album per day, usually given in 4-hourly doses until the pyrexia subsided. Thereafter treatment was continued for a varying period, and in this connection a case out of a series reported by Breen and Taylor (1937) is of interest. A young female patient responded so well to treatment that the drug was stopped after 3 days, but on the 10th day in hospital she suffered a relapse which responded equally well to further treatment. Several such cases are reported elsewhere, and it therefore seems advisable to continue treatment until the symptoms have subsided completely, usually a period of from 6—10 days. In some cases combined treatment, Prontosil Soluble together with one of the oral drugs, was used, while in others Prontosil Soluble alone was given.

The Disease in Children

It is well known that erysipelas in infants is a serious disease which often ends fatally and in which relapses are common. Several physicians, among them Gmelin (1935), Püschel (1935), and Maraun (1936), have reported good results following Prontosil treatment in this condition ; the infants' ages varied from a few days to 18 months old. Very young babies were given 0.08 g. Prontosil 3 or 4 times daily, older infants 0.15 g. twice or thrice daily, and older children received 0.3 g. twice or thrice daily, the dose being reduced but continued for a few days after

the temperature fell. Meyer zu Hörste (1936) pointed out, in this connection, that it might be necessary to give HCl in infants before Prontosil (especially P. Rubrum) became effective; he recommended the administration of 6 drops of acid. hydrochlor. dil. with each tablet.

5. Cellulitis and Lymphangitis

One of the first cases of cellulitis treated with Prontosil, which may become of historic interest, was reported by Domagk (1936), whose daughter was attacked by a severe and rapidly spreading cellulitis after running a needle into her hand. Despite surgical intervention she became stuporose and as no further surgical measures were possible Prontosil was used. The patient made a complete recovery.

Sigel (1936) employed Prontosil Soluble and occasionally Prontosil Rubrum in several patients with abscesses, boils, and cellulitis. The treatment was effective in cellulitis and abscesses, but the drug did not always prevent the formation of pus. He suggested that Prontosil might be useful as a prophylactic in the treatment of infected or dirty wounds, and gave it from the start in some cases of heavily contaminated wounds, obtaining primary healing. A different report (unpublished) gave the results of treatment in 119 cases, comprising furunculosis, carbuncles, abscesses, cellulitis, lymphangitis, mastitis and erysipelas; in the 32 cases of cellulitis striking effects were noted, the clinical condition improving and the temperature falling 24—48 hours after the institution of Prontosil treatment. In the case of furuncles, abscesses, and carbuncles the course appeared to be more rapid than usual, and the inflammatory induration surrounding the pus cleared up more quickly. In this report it was stated that in some cases where Prontosil Album failed to achieve an effect Prontosil Rubrum was successful.

6. Scarlet Fever

Few reports on the use of Prontosil and related compounds in scarlet fever are available, and this may be due to the fact that, for some years, scarlet fever has been a relatively mild disease in which, in many cases, no treatment was required. On the other hand collected experience to date suggests that the action of the drug in this disease is at best doubtful, and that it should not be regarded as a substitute for serum.

Hogarth (1937), using para - benzyl - amino - benzene - sulphonamide in scarlet fever, could detect no significant improvement in the treated group of cases as opposed to control groups, but Peters and Havard (1937), using the same compound, noted

that complications occurred in 84 per cent. of the cases (in some of which serum was used) as against 35 per cent. in the test cases. Long and Bliss (1936), using sulphanilamide, also reported successful results in 19 cases, one of which, a girl with cervical adenitis and otitis media in whom the temperature fell to normal in 24 hours, was particularly impressive. Massingham (1937) described a recovery from septicæmia appearing on the fourth day of an attack of scarlet fever.

While, on the basis of existing reports, Prontosil cannot be recommended in mild cases of scarlet fever, it should be given in cases complicated by otitis media or nasal discharge and, as Prontosil has shown itself most successful in virulent infections, having little effect on such conditions as bacterial endocarditis caused by the streptococcus viridans, it is possible that the drug may prove of great value in severe cases of scarlet fever in which the temperature is extremely high and anginal signs are very marked. These possibilities, however, await further elucidation. Prontosil can be given to patients suffering from post-scarlatinal nephritis, if necessary, but as the drug is excreted in the urine it is advisable to give a dose somewhat smaller than would be given to a healthy patient.

7. Gas Gangrene

Only three cases of gas gangrene treated with sulphanilamide have been reported, by Bohlman (1937). In each instance the infection appeared one to five days after compound fracture of the lower limbs had been sustained, although all three patients had received a prophylactic injection of gas gangrene antitoxin.

In the first two cases treatment was begun with 1 and 1.5 g. sulphanilamide respectively, given six-hourly in the first and four-hourly in the second, for two days. During the second day of treatment the temperature fell to normal in both cases, the toxic symptoms disappeared, and the patients appeared fairly well. In the third case treatment was begun with 1.2 g. sulphanilamide every four hours, and treatment was continued with a varying dosage for six days, after which it was discontinued. The temperature did not fall until the seventh day and was not normal until the twenty-sixth day. All three patients made a good recovery, but it is interesting to note that in the first two the recovery was complicated by an appearance of osteomyelitis.

A conclusion on the efficacy of sulphanilamide in this infection is not justified by such a small number of cases, but it must be admitted that in a disease with a mortality-rate in the region of 50 per cent. recovery in three consecutive cases is unusual.

8. Typhoid Fever

It is possible that Prontosil may prove of value in the treatment of typhoid fever, as it was shown by Buttle et alii (1937) that para-amino-benzene-sulphonamide protected mice against multiple lethal doses of *B. typhosus* and *B. paratyphosus B.* So far the only clinical trial is that reported by Schmidt (1936), who used Prontosil with apparent success in three patients suffering from enteric. Barker (1937) reported an interesting case in which a seaman who suffered from *B. typhosus* pyelitis was treated with sulphanilamide, 0.5 g. twice daily by mouth for five days. Thereafter no organisms could be detected in the urine, but a positive culture was obtained nine days later, and the same dose of sulphanilamide was given for 14 days. Four cultures made during the next five weeks failed to grow typhoid bacilli.

9. Tuberculosis and Syphilis

No work on Prontosil in tuberculosis has yet appeared, and it can be said, from unpublished reports, that Prontosil appears to have no effect upon tuberculosis of the lung. In some cases, however, a good effect on secondary streptococcal infection in patients suffering from tuberculosis has been observed. Campbell (1937) investigated the action of sulphanilamide on syphilis in the rabbit, and could not detect any diminution in the number of spirochætes or in the development of the disease while sulphanilamide was being given.

Chapter V.

GENITO-URINARY INFECTIONS

1. Pyelitis and Cystitis

Shortly after the introduction of Prontosil in Germany it was found to produce striking results in pyelitis in infants. The first report was issued by Temming (1935), who treated three infants suffering from this disease; in all three cases the temperature fell and the general condition improved rapidly, the urine becoming free from leucocytes and albumen within a few days.

Continental Experience

Later on, Pernice (1936) recorded the treatment of 18 children of varying ages with Prontosil Rubrum tablets given in milk or tea. The dosage in infants was 0.1 g. thrice daily, small children received 0.15 g. thrice daily, and in older children the dosage was from 0.3—0.7 g. per day. Treatment was continued for from three to four weeks. There was only one failure in this series and in other cases the urine became normal in from four to twelve days. Two relapses necessitated a further course of treatment. Maraun (1936) and Huber (1936) also achieved good results in infants and young girls suffering from *B. coli* pyelitis. In some of the observers' cases vomiting occurred, and Klein (1936), as a prophylactic measure, recommended the administration of glucose along with the Prontosil. These reports dealt with the effect of Prontosil in *B. coli* infection in childhood, but Weiser (1937) achieved cures in severe urinary infections with other organisms, and Klose (1936) successfully treated two adult patients with Prontosil: one was a woman with cystitis, and the other a man with symptoms of pyelitis and an acute staphylococcal urethritis; both patients recovered in ten days' time.

A Group of English Cases

Excellent results were reported by Kenny and others (1937), who used Prontosil Album in amounts of 1.5 to 1.8 g. daily for five to seven days in 46 cases of *B. coli* urinary infection. Since the authors anticipated a gradual decline in the infection, it was decided at the start that bacterial counts of the urine should be made on repeated occasions; but when it was discovered that the

urine became sterile in almost all instances on the second examination the bacterial count was omitted.

Of the 16 patients with pyelitis of pregnancy 12 were suffering from a first attack in the acute stage, and in five of those who showed signs of pre-eclamptic toxæmia Prontosil brought about no aggravation of the condition. In all cases the temperature and pulse rate fell to normal in 48 hours and the urine became free from pus and albumen in from two to five days. Relapse with clinical symptoms did not occur in any of the cases, although one patient who had previously had her first pregnancy terminated because of repeated attacks of pyelitis was included in the series ; in six instances, however, symptomless bacteriuria was detected. Seventeen patients with pyelitis in the puerperium responded equally well to Prontosil treatment, although one developed a clinical relapse. In addition to these acute cases, nine patients, most of whom had chronic cystitis (in some cases of months' or years' duration) were treated before or after operation. Considering the persistence of such infections it is remarkable to note that in these cases the urine was sterile in an average of three days. Of the remaining four patients treated, one with disseminated sclerosis was not only freed from infection (although *B. Proteus vulgaris*, which was present, was more resistant to Prontosil than *B. coli*), but was improved as regards dysuria and incontinence. The other two patients, who were also rapidly relieved, had suffered from pyelitis which had resisted mandelic acid treatment for several months ; the fourth was a case of acute cystitis which responded rapidly and permanently to Prontosil.

A large number of bacteriological tests was carried out on the urine of patients who had received Prontosil, and while on the whole it was shown that the bactericidal power of the urine was roughly proportional to its Prontosil Album content, it was also shown, in some instances, that organisms recovered from patients who had responded to treatment with the same rapidity as others were much more resistant to the in vitro tests. It was considered that this " therapeutic efficiency beyond that indicated by the in vitro tests " might be accounted for by the action being partly bacteriostatic in the tissues, as well as being directly bactericidal in the urine.

In one case—that of a pregnant woman of thirty with an atypical *B. coli* urinary infection—no form of treatment, including Prontosil, was successful in sterilising the urine. Intravenous urography showed no abnormality beyond dilated ureters, and two months after delivery the infection was still present.

Prospects of the Treatment

A number of interesting points emerged from the above survey. It showed that Prontosil, even in small doses, could be

expected to produce a cure in the vast majority of cases of cystitis and pyelitis due to the *B. coli*, and that the sterilisation of the urine occurred with unexpected rapidity. Moreover, the treatment was apparently without ill-effect in toxæmia of pregnancy, in pregnancy itself, and on the unborn child. (In this connection it should be noted that the author recovered Prontosil from the amniotic fluid in one case.) As against mandelic acid Prontosil had the advantages of simplicity of administration, greater tolerability in pregnancy, and cheapness. A further point, mentioned by Helmholtz (1937b), is that, unlike mandelic acid and hexamethylene tetramine, Prontosil is effective in both acid and alkaline urine.

Whether or not Prontosil Album has an effective action in urinary infections with organisms other than *B. coli* is not settled, but Becker (1937) reported that the results of Prontosil treatment in staphylococcal pyelocystitis were almost always favourable. Buchtel and Cook (1937), who reported good results in bacilliary infections, found that coccal infections were more difficult to influence, while no improvement was obtained in infections with the *Streptococcus fæcalis*, an observation supported by Helmholz (1937a and b), who also investigated the effect of pH value of urine on bactericidal activity. He concluded that sulphanilamide was apparently more active in an alkaline urine, and noted good results in *B. proteus ammoniæ* infections; he also pointed out that Prontosil could be safely used in patients with diminished renal function, a condition which militates against the efficiency of other urinary antiseptics.

2. Urethritis and Prostatitis (including Gonorrhœa)

In most cases of urethritis and prostatitis the infection is gonococcal in origin, although secondary infection with other organisms is extremely common. In some instances, however, a urethritis may be caused by a staphylococcal infection, and the occurrence of infection preceding or following prostatic operations is well known.

From this point of view Buchtel and Cook (1937) concluded, after using sulphanilamide in the treatment of over 200 patients with urinary infections, that it was the most effective drug yet discovered for sterilising the urine before prostatic surgery. These observers treated one group of prostatic infections with mandelic acid, and another group with sulphanilamide : 50 per cent of the first group yielded positive cultures from the prostatic secretion after treatment, whereas in the sulphanilamide group only one culture was positive out of 24. In addition, 31 patients with gonorrhœa (21 men and 10 women) were treated with sulphanilamide; two men and two women were classified as failures.

A preliminary report on sulphanilamide in gonorrhœa was next published by Dees and Colston (1937), who treated 47 patients. The dosage was 4.8 g. daily (in four doses) for two days, 2.6 g. daily for three days, and 2.4 g. for from four to eight days. No other treatment was given; in all cases the progress of the disease was checked, but three cases failed to respond, and in another three cases which responded promptly a recurrence occurred. Five other patients were rendered free from symptoms but the gonococcus was still discoverable in the urethra. In the remaining 36 cases the gonococci and the discharge disappeared in less than five days.

English Experience in Gonorrhœa

Even more striking results were reported by Crean (1937), who treated one hundred cases of gonorrhœa with Prontosil Soluble, and an emulsion of sulphanilamide containing 0.5 g. per drachm, along with routine irrigations. Only six of the patients failed to respond—in all these the disease was in the acute stage—while no failures occurred in the eight patients suffering from non-specific urethritis or chronic gonorrhœa. Only two patients relapsed. The author concluded that in favourable cases cure was obtainable in a little over 17 days, and recommended for administration during that period 52 g. sulphanilamide and 40 c.c. Prontosil Soluble. Anwyl Davies (1937) had previously published his adverse report on the use of Prontosil in gonorrhœa, and Cokkinis (1937), while disagreeing with Anwyl Davies on this point, stated that Crean's figures were too optimistic, as the period of test had not been sufficiently long. None the less Cokkinis concluded, after treating 250 cases, that "we now possess an effective remedy for gonorrhœa and for most of its complications."

The latter found that a small group of cases completely failed to respond to treatment; in the large majority of acute and chronic cases, however, cure was attained in a week or less. He stressed the importance of close supervision, and the necessity of keeping the period of treatment within 21 days, with a total dosage not exceeding 60, or at the most 70 g. In the healthy adult with acute gonorrhœa the dosage recommended was 4 to 5 g. daily for two to five days, followed by 3 g. daily for a further seven days. The effect obtained with a smaller dosage (3 g. daily for seven to ten days followed by 1.5 g. daily for the same period) in cases of chronic gonorrhœa and non-specific urethritis was even more striking; no case of non-specific urethritis failed to respond to treatment. In order to keep the concentration of sulphanilamide as constant as possible it was recommended that the drug should be given in four daily doses.

Several further reports were presented at a meeting of the Medical Society for the Study of Venereal Diseases (1937) by Hanschell, King, Harkness, Lloyd, Johnson, Rawlins, MacElligott, and Anwyl Davies (1937); and Brown (1937) also stated at this meeting that the majority in a small series of cases of vulvo-vaginitis treated with Prontosil Album reacted well, the profuse discharge disappearing within two or three days, but that the full six months' period of observation had not elapsed at the time of the discussion.

Dosage

No definite scheme of dosage can be arrived at from a consideration of the above reports, and it is difficult to decide, at the moment, whether local treatment should accompany Prontosil therapy. Further uncertainty with regard to the optimum time for Prontosil treatment has arisen because of Felke's suggestion (1937), which is supported by other observers, that the chemotherapeutic drugs act more efficiently if the disease has existed for a fortnight before treatment, enabling the tissues to acquire a resistance to the infection and a readiness to attack it. It would appear wise, however, to begin treatment with fairly large doses (4 to 5 g.) in suitable cases, and if no response is obtained within a few days to cease treatment, as the response is usually striking in favourable cases. It should be noted that the results in chronic gonorrhœa and non-specific urethritis have been extremely favourable.

3. Chancroid

The successful treatment of 20 cases of chancroid with Prontosil Soluble was described by Hanschell (1938), who stressed the ineffectiveness of other methods of treatment. Each patient received one or two further injections of 10 c.c. at three-day intervals; in addition Prontosil Album, 3 g. daily in divided doses, was given. The ulcers healed rapidly and the buboes subsided in from five to ten days.

Chapter VI.

RESPIRATORY AND CIRCULATORY INFECTIONS

1. Pneumonia

Scheurer (1936) noted a rapid defervescence, and improvement in the pulmonary condition, in a case of streptococcal pneumonia treated with Prontosil. No extensive investigations into the use of Prontosil in pneumococcal conditions, however, have been reported, although animal experiments have shown that Prontosil has some effect in Type III pneumococcus infection, and recoveries from pneumococcal meningitis have been recorded.

In the only series of cases of pneumonia (Type III) so far reported, Heintzelmann and others (1937) used Prontosil Album and occasional injections of Prontosil Soluble. The 19 cases were divided into two groups, nine patients being treated and ten being used as controls. The treated group was slightly favoured, as the untreated group included a case of asthma, a case of slight myocarditis, and an alcoholic; moreover, the average age of the treated patients was 44.4, that of the untreated being 49.2. In the treated group the two oldest patients, aged 60 and 70, died, while in the untreated group only two, aged 31 and 39, recovered. Comparison was also made with 33 other cases of Type III pneumonia occurring at the same time in Pittsburg, but not observed by the authors. In that series 9 recovered and 24 died. The mortality for the patients treated with Prontosil was 22 per cent., and for those treated in the usual way 74 per cent. In view of their results, the authors suggested the continuance of treatment of Type III pneumonias with Prontosil until "a sufficient number of cases has been accumulated to justify a final judgment as to the efficacy of this mode of therapy."

2. Influenza

A substance closely related to the coloured Prontosils was used by Herluison (1937), who had, in a series of 300 patients with influenza (1935—1936), 22.7 per cent. of complications such as pneumonia, empyema, and meningitis. In the next series of cases, 717 in number, treatment with the drug was begun at an early stage, and the incidence of complications was 3.1 per cent. In the first series 7 patients died, and no

deaths occurred in the second. In view of these findings, and in view of the fact that deaths from influenza generally follow a virulent secondary infection, possibly streptococcal in nature, a further trial of Prontosil during epidemics is indicated.

3. Empyema

Fleming (1937) reported a case of empyema, treated with sulphanilamide given by mouth, in which the drug appeared to bring about an improvement. The use of Prontosil in streptococcal empyema was described by Tilling (1936), who injected 5 c.c. of Prontosil Soluble (2.5 per cent.) into the pleural cavity after aspiration of the purulent contents. This was done every 2 or 3 days, and cure resulted in from 7—22 days. Brown (1937) attributed the good results obtained in 2 cases of streptococcal empyema following influenza almost exclusively to the use of Prontosil. Both patients were in a poor general condition, and in both a positive culture for streptococcus was obtained from the pleural fluid ; the first patient received Prontosil by mouth, and, with a view to diminishing the infectivity of the pleural fluid, 5 c.c. of 2.5 per cent. Prontosil Soluble was injected into the pleural cavity. When repeated in three days' time the fluid became sterile, a similar result being achieved in the second case.

The advisability of this mode of treatment is, however, on experimental grounds, uncertain, for Nicholson (1938), who investigated the action of Prontosil Soluble in streptococcal empyema in rabbits, reported that the treated animals died earlier than the controls and in no case was the empyema rendered sterile. Further clinical investigations would appear to be desirable.

4. Endocarditis

The only important infection of the circulatory system, apart from pericarditis, is endocarditis, but very few favourable results from Prontosil treatment in this disease have been recorded. This is largely due to the fact that the most common cause of this disease is the *streptococcus viridans*, an organism which (at any rate in vivo) appears to be unaffected by Prontosil. Gantenberg and Thimme (1935) claimed cure in one case of septic endocarditis following tonsillitis (organism not stated), but achieved no result in a case of *streptococcus viridans* endocarditis and septicæmia. Similar failures in this respect have been reported by other observers, although in some cases (unpublished) Prontosil has appeared to cause a diminution in temperature and a temporary improvement in the patient's well-being. The possibility of successful chemotherapeutic treatment for this disease therefore belongs to the future.

Chapter VII.

INFECTIONS OF NERVOUS SYSTEM

Meningitis

When the first successful results of Prontosil therapy in puerperal sepsis in this country were under consideration, it was suggested that a diminution in virulence of the hæmolytic streptococcus might have been partly responsible for the improved mortality and morbidity figures obtained, and a similar explanation for many of the early successes in other diseases of a fluctuating character, such as erysipelas, might have been considered possible. Pyogenic meningitis, however, and especially that variety caused by the hæmolytic streptococcus, offered a test case for the Prontosil group of drugs in which definite conclusions were possible ; there was no need for controls or for analysis of the results according to symptoms and signs, since for years the almost invariable ending in such cases had been death. The therapeutic activity of Prontosil, as recoveries occurred, was thus clearly shown.

The death-rate for streptococcal meningitis, according to Gray (1935), Tripoli (1936), Zeligs (1935), Neal et alii (1937), and Schwentker, Clason et alii (1937) ranged from 91.6 per cent. to 100 per cent. up to 1936, when the new drugs were first used in this condition.

Streptococcal Cases

Since then, out of 39 cases proved by culture to be due to the hæmolytic streptococcus and treated with Prontosil or sulphanilamide, 32 (82 per cent.) recovered, and recovery also occurred in 11 out of 14 (78.5 per cent.) of the doubtful or non-hæmolytic cases. Many patients received serum treatment in addition, while some were given blood transfusion ; but if the poor results previously achieved by these methods of treatment are considered it must be concluded that the Prontosil or sulphanilamide was mainly responsible for the remarkable figures mentioned.

These cases were reported by the following observers (and others mentioned in the text) : Anderson (1937), Arnold (1937), Basman and Perley (1937), Caussé et alii (1936), Cawthorne (1938), Davel (1937), Draeseke and Rayner (1937), Frazer (1937), Hagemann (1937), Lallemant and Pollet (1936), Le Mée and Salomon (1936), Love (1938), Lucas (1937), McQuarrie

(1937), Martin and Delauney (1937), Millett (1937a), Rouget and Vaidie (1936), Thompson (1937), Trachsler et alii (1937), and van Nieuwenhuyse (1936).

Most of the patients suffered from mastoid disease ; in some the meningitis followed operation, and in others operation was performed after the meningitis had begun ; in a minority the disease followed trauma or had no obvious cause. In most instances the response to treatment was prompt, and in some the authors stressed the almost miraculous nature of the cures obtained ; one patient, reported by Weinberg et alii (1937) was almost moribund when treatment was begun, and Vitenson and Konstam (1937) remark of a recovered case that " the moribund condition of the patient after operation led one to expect a fatal issue." Occasionally the patient's condition fluctuated, but one feature which illustrates the remarkable effect of the drug is that the cerebro-spinal fluid from which hæmolytic streptococci had been cultured became sterile in from 24 hours up to, in Carey's case (1937), 7 days. In one instance not yet reported this result led to an accusation on the part of the pathologist that the second specimen had not come from the same patient as the first !

In the most recent case, reported by Smith et alii (1938), a girl of 21 developed meningitis due to an anaerobic hæmolytic streptococcus four weeks after the first attack of otitis media. The treatment was begun with Prontosil Soluble and continued with sulphanilamide, and apart from a regression in her condition when the drug was suspended for two days because of cyanosis she made a perfect recovery.

Meningococcal Cases

The results of Prontosil and sulphanilamide treatment in meningococcal meningitis have been as striking as in the streptococcal group ; 25 recoveries (96 per cent.) were recorded in 26 cases, and in a recent report by Eldahl (1938) the mortality-rate was given as 25 per cent. These cases were reported by Armand-Delille (1937), Jennings and Southwell-Sander (1937), McIntosh et alii (1937), and Pongratz (1937), in addition to the authors mentioned in the text. Most of these patients were given anti-meningococcal serum, in some blood transfusion was performed, but in 5 reported by Carey (1937) no other treatment was used. The response to treatment was again prompt and striking—one case (Bernstein, 1937) being " almost moribund "—and again the cerebro-spinal fluid became sterile in from 24 hours to 3 days. In some instances, according to Schwentker, Gelman and Long (1937), a negative culture was obtained after the first intrathecal injection of sulphanilamide.

Pneumococcal and Other Infections

A small number of patients with meningitis due to other organisms has been treated with chemotherapeutic drugs. In 16 cases of pneumococcal meningitis (Caldwell and Byrne—1937), Latto (1938), Mertens and Mertens (1937), Millett (1937b), Neal et alii (1937), 6 recovered (37.9 per cent.) and while the number is too small to permit of definite conclusions, these recoveries are striking in view of the fact, stated in Price's Textbook of Medicine (1937), that a recovery from this disease has never been recorded. Moreover, Basman and Perley, who treated three cases with one recovery, remarked of this patient that " this case was the first of pneumococcal meningitis proved by culture to recover in St. Louis Children's Hospital ". Considering the 2 fatal cases they stated that one died 15 hours after admission, while the other should have had more intense intrathecal treatment. Jones (1937) reported recovery in a case of influenzal meningitis following sulphanilamide treatment, and in 6 cases of this disease reported by Carroll and Willoughby (1937), Hageman (1937), Macintosh et alii (1937), McQuarrie (1937), and Basman and Perley (1937), another recovery occurred. The latter observers also reported a recovery in meningitis caused by the *Bacillus proteus*, and Nader (1937) reported 2 cases of *B. coli* meningitis in children with one recovery on Prontosil treatment.

Staphylococcal Infection

With regard to staphylococcal meningitis, in which the mortality-rate is extremely high, a remarkable case has been reported by Bloch and Pacella (1938). The patient was an infant 17 days old who had had a meningocele removed 11 days previously. Thirty-six hours before admission the site of operation became inflamed and the infant became irritable and apathetic. Staphylococci were cultured from the c.s.f. Sulphanilamide was given intrathecally and orally from the first day, and in 11 days the c.s.f. culture was negative. A total of 10 g. sulphanilamide was given over a period of 27 days, and the infant recovered.

Gonococcal Meningitis

One case of this condition, in which sulphanilamide was used, has been reported by Marven and Wilkinson (1938) ; and they noted that in 22 cases already reported the meningitis developed following active gonococcal infection elsewhere in the body. In the case they describe, symptoms of meningitis appeared some two weeks after the commencement of the

gonorrhœal urethral discharge. Sulphanilamide was used, but the authors did not consider it proved that recovery was due to the drug.

Opinions re Route of Administration

In the section of pharmacology (page 9) it was mentioned that all three Prontosils were excreted into the cerebro-spinal fluid, in all probability achieving an efficient therapeutic concentration there after parenteral or oral administration. In spite of this fact, however, the drug has been given by every possible route in the treatment of meningitis. In some instances Prontosil Rubrum and Prontosil Album were successful when given orally, but in the case reported by Thompson (1937), a patient who failed to improve on oral treatment recovered following the intramuscular injection of Prontosil Soluble and a transfusion from a donor who had had Prontosil treatment, while in another partly recovered case of pneumococcal meningitis (Basman and Perley, 1937) the temperature rose and the c.s.f. culture, previously sterile, became positive again with the suspension of intrathecal and intramuscular medications, and the continuance of oral treatment 4 g. per day.

Eldahl (1938) came to the conclusion that intrathecal treatment was much more valuable in meningococcal meningitis than oral and parenteral administration, but Willien (1938), who successfully treated five patients suffering from meningococcal meningitis with sulphanilamide (additional to those mentioned above), apart from a preliminary subcutaneous injection of the 0.8 per cent. solution, gave the drug solely by mouth. Two of his patients had received prolonged treatment with antimeningococcal serum without benefit, and in a third case in which the meningitis recurred because of insufficient sulphanilamide treatment the patient was readmitted to hospital and cured by a further course of sulphanilamide.

It appears advisable, therefore, to use parenteral and oral administration together, whenever possible ; in many patients oral administration is impossible because of the symptoms of the disease. As regards intrathecal administration a difference of opinion exists, but in any event this route is indicated in serious cases which show no signs of improvement with other methods of administration. According to Schwentker et alii the intrathecal Prontosil Soluble appeared to irritate the meninges, but Le Mée and Salomon gave a related compound intrathecally without ill-effects. Moreover Millett (1937b), who carried out a post mortem on a fatal case of pneumococcal meningitis treated with Prontosil Soluble, found the drug distributed throughout all the tissues of the nervous system

without any trace of irritation or injury from its presence. Other workers have used a 0.8 per cent. solution of Prontosil Album. Whatever drug is used for intrathecal administration, it must be given slowly and by gravity.

Dosage Used

The dosage was as variable as the method employed, but, speaking generally, high doses were given. Basman and Perley gave a first dose of 0.2—0.25 g. sulphanilamide per kilo of body-weight, followed by the same amount given daily in divided doses ; while Schwentker, Clason et alii gave 1 g. per 20 lbs. of body-weight, with a maximum of 5 g. per day. Prontosil Soluble was given in doses of $\frac{1}{2}$ c.c. (5 per cent. solution) per lb. of body-weight per day ; while, using the 0.8 per cent. sulphanilamide solution, the dosage for 40 lbs. was 100 c.c., for 40—80 lbs. 200 c.c., for 80—120 lbs. 300 c.c., for 120 lbs. and over 400 c.c. They continued treatment at the above level until the patient had improved and the c.s.f. had been sterile for 48 hours, whereupon sulphanilamide was given orally at one-third of the previous dosage for a further 7—14 days.

It cannot be claimed as yet that Prontosil treatment has superseded antimeningococcal serum or obviated the necessity for operation in all cases of streptococcal meningitis, but the results so far obtained show that the drugs should be given in large doses, as early as possible, in all cases of purulent meningitis.

Chapter VIII.

MISCELLANEOUS INFECTIONS

1. Mouth, Ear, Nose and Throat Infections

The position of Prontosil in ear, nose and throat infections, which are frequently of streptococcal origin, is at present ill defined. This largely arises from the fact that no one has studied the effect of the drug in a large series of cases at various stages, so that it is not possible to decide, for example, whether or not Prontosil would make operation unnecessary in cases of mastoid infection treated sufficiently early. Numerous publications, however, mention good or striking results in infections of this region. Thus Palmer (1937) and Lyth (1937) each reported a recovery from *Ludwig's angina* following dental operation. Both patients were seriously ill with high temperatures and rigors, and three days after the Prontosil treatment was begun the temperature was dropping in each case, and improvement began. Guirdham (1937) also reported a recovery in a severe case of *septic parotitis* in a mental patient under Prontosil treatment.

Tonsillitis

Klee and Römer (1935) obtained excellent results in severe tonsillitis which was sometimes associated with lymphangitis and thrombophlebitis. After the inauguration of Prontosil it was never found necessary to ligature the jugular vein, nor has any death from these conditions been recorded. In a small series of cases of acute follicular tonsillitis treated with Prontosil Rubrum, Perkins (1937) demonstrated that the treated cases required a shorter period of hospitalisation and a shortened course of convalescence, compared with the untreated cases. Further experiences were reported by Hageman (1937) who stated that "the immediate therapeutic result was excellent in seven cases, but beta-hæmolytic streptococci persisted in throat cultures in some instances as long as four and five weeks." Brenneman (1937), who made the interesting observation that "in two cases of erysipelas the result was so prompt as to be positively shocking," also noted that in cases of hæmolytic streptococcal throat carriers, while the culture promptly became negative on sulphanilamide treatment, it became positive again one to six days after the drug was stopped.

Brenneman also treated 14 cases of aural infection with sulphanilamide, the patients' ages varying from 18 months to 12 years. All of them had *otitis media*, in some cases acute, accompanied by fever, in others chronic; signs of *mastoiditis* were present in 5 cases, and in 2 a mastoid operation was performed. Ten of these 14 patients responded favourably to sulphanilamide treatment, the discharge drying up in from one to seven days, although in some a slight discharge returned. In 3 patients mastoid tenderness was present, and this cleared up along with the aural discharge. Somewhat similar results were reported by Bernstein (1937) and Macintosh et alii (1937).

Few results with *sinusitis* have been reported, but Roberts (1937) treated a female patient who developed streptococcal pansinusitis after recovering from scarlet fever; both middle and superior meatuses were filled with the sero-purulent discharge, she had pain over the head and face, and the left side of the face was swollen. On the second day of infection she was given 30 c.c. of Prontosil Soluble, and on the third day she received 3 g. Prontosil Album. Thereafter the pain and discharge disappeared, and the patient felt completely well. The author stated that this was the most rapid recovery from a post-scarlatinal sinus infection he had ever seen, and in the same publication reported good results in a case of *quinsy*, one of mastoiditis with possible sinus thrombosis, and one of severe otitis media.

From the scattered and scanty reports which have appeared it may be concluded that Prontosil is of value in acute hæmolytic streptococcal infections of the mouth, ear, nose and throat. In chronic infections, however, although good results have been reported, several failures have also occurred; because of this, and the well-known difficulty of dealing with established and long-standing cases of sinusitis and otitis media, Prontosil treatment should be begun as early as possible, even in very young patients. In all probability, moreover, the use of Prontosil in patients being prepared for, or recovering from, mastoid operations is advisable.

2. Eye Infections

The value of Prontosil in *cellulitis* and *erysipelas* of the eyelids and surrounding skin has been stressed in numerous publications, but at the moment no large series of cases of pyogenic disease of the eye itself treated with this drug is available. Prontosil was used in a case (unpublished) of *ophthalmia neonatorum*, both

local and general treatment being given, with success. Harrie (1938) also reported a striking result with sulphanilamide in *panophthalmitis*. Four patients with this disease were treated, and in 2 the eye was saved. In the remaining 2 cases, although the condition improved rapidly, the eye was shrunken and ultimately had to be enucleated. Sympathetic ophthalmia did not occur in any of the cases.

3. Diseases of Joints

In acute infections of the joint cavity, in which organisms are cultivated from the synovial fluid, Prontosil may be found valuable in suitable cases. Clinical reports in this connection are scanty, but Smith (1937) reported recovery with complete restoration of joint function in 2 cases of *hæmolytic streptococcal arthritis* of the hip-joint treated with Prontosil, and Keefer et alii (1937) treated 2 cases of *gonococcal arthritis* with sulphanilamide; within two days the gonococci had disappeared from the synovial fluid of 2 cases in which a positive culture had previously been obtained.

Rheumatic Fever

As focal streptococcal infection is supposed to play an important part in the ætiology of rheumatic fever and some forms of chronic rheumatism, it might be expected that Prontosil would exert a beneficial effect in such cases. So far, however, the reports available contradict this view. Thus, Massell (1937) investigated the effect of Prontosil treatment in 6 cases as against 6 controls; all 12 were patients who had suffered from rheumatic fever and in whom throat cultures were positive for hæmolytic streptococcus. In no case did Prontosil have a beneficial effect, and the duration of positive throat culture for the hæmolytic streptococcus averaged 16 days in the Prontosil group and 18 days in the control group. A further series of 8 patients showing all the manifestations of rheumatic fever, except chorea, were treated by Swift et alii (1938) with sulphanilamide. In no case did the drug have a favourable influence, and, in some instances, toxic effects were marked. The appearance in some of the patients of subcutaneous nodules during sulphanilamide treatment was taken to indicate that the drug was completely ineffectual. In view of the fact that Prontosil-treated patients who have recovered from puerperal sepsis have continued to excrete hæmolytic streptococci in the vaginal discharge, the authors considered it highly probable that the infected foci were uninfluenced and that the bacterial toxins continued to be elaborated therefrom.

Rheumatoid Arthritis

The experiences of Gantenberg and Thimme (1935) were somewhat different. They reported complete failure in a case of acute rheumatic fever, as more joints became involved during the treatment with Prontosil. On the other hand, 8 cases of chronic and acute recurring arthritis, 2 cases of chronic infective arthritis and a case of sub-acute recurring rheumatoid arthritis, were considerably relieved and, in some cases, a cure was produced. This, in the authors' opinion, supported the view that genuine rheumatic fever was not caused by streptococcal infection, and that Prontosil should be of value in making a differential diagnosis between arthritis of infective origin and specific rheumatic fever. One case of great clinical interest was included in this series. The patient suffered from chronic infective arthritis and psoriasis, the two conditions spreading and developing at the same time: short periods of Prontosil treatment brought about temporary improvement and a final course of two months' duration produced a complete disappearance of both conditions. Great improvement in a sub-acute case of rheumatoid arthritis was also reported by Recknagel (1935) using Prontosil Rubrum. These conflicting reports make further work in this direction desirable.

4. Skin Infections

Prontosil was first used in dermatological conditions by Jaeger (1936), who employed Prontosil Rubrum tablets in a saturated solution in equal quantities of alcohol and acetone for application to the skin, and Prontosil Soluble (with or without 10—20 per cent. glycerine) for application to the mucous membrane. Both these preparations were also used in ointment form—2 per cent., 5 per cent., 10 per cent. and 20 per cent. The best results were achieved in infections of the axillary sweat glands, furunculosis and folliculitis, while some cases of dermatitis responded well. In *psoriasis* no actual cures were obtained. The solution was also used as a paint and gargle in inflammatory conditions of the pharynx and in leucorrhœa. Merz (1937) then published a somewhat different formula. He used Prontosil ointment, which was made by crushing Prontosil Album tablets, suspending in water, filtering and working into a 10 per cent. ointment with gelatine and glycerine. He claimed excellent results in *folliculitis*, *furunculosis*, *acne*, and *impetigo contagiosa*; in some cases Prontosil tablets were given simultaneously with the local treatment. Scherber (1936) also stated that Prontosil had some effect in 2 cases of *pemphigus vulgaris*, but Muzger (1936) could not obtain any improvement in a patient with this disease although,

as did Fidanza (1936), he noted an improvement in a case of *dermatitis herpetiformis*. Improvement in 3 cases of *lupus erythematosus* was reported by Linser (1938) who used Prontosil on cases in which other means had failed to bring about a cure.

5. Tropical Diseases

Undulant Fever

Berger and Schnetz (1937), Suchier (1937), and de Millas (1937) each treated a patient with undulant fever ; in the first case Prontosil by mouth (i.e. Prontosil Rubrum) and Prontosil Soluble were used, in the second Prontosil Rubrum alone, while the third received daily injections of Prontosil Soluble only. Within a week the temperature had fallen to normal in all three cases and no relapses occurred. Ahringsmann (1937) reported another successful case. Richardson (1938) also treated 2 cases ; in the first, a man of 46, the temperature fell after six days' treatment with 0.6 g. Prontosil Album twice daily, and an injection of 5 c.c. Prontosil Soluble (5 per cent.) on each of four consecutive days. This case was of interest in that some four weeks later the symptoms returned, and were relieved by Prontosil treatment as quickly as on the first occasion ; since then there have been no signs of relapse. The second patient's temperature fell on the fourth day of treatment. Francis (1938), in addition to reporting 2 similarly striking cases in both of which the temperature fell within five days of treatment with 3 g. sulphanilamide daily, carried out some in vitro tests with the organisms recovered from case 1. These tended to show that the *Brucella abortus* was considerably more susceptible to the action of sulphanilamide in vitro than was the pyogenic streptococcus under the same conditions. Apparent successes in this direction were also described by Lloyd (1938), Matthews (1938) and Page (1938). These clinical and bacteriological findings indicate that further trials of Prontosil in this disease are desirable.

Lymphogranuloma Inguinale

Two publications are of interest in this connection. In the first, Gjuric (1938) used Prontosil Rubrum and Fouadin in combined treatment. The Prontosil was given for a five-day period in doses of 2.5 g. daily, immediately followed by a further three-day administration of 2 g. daily—pause of 3—5 days, and then repetition of course. The number of Fouadin injections necessary was reduced from 10—15 to 3—10 (Khalil's scheme), and rapid and satisfactory results were obtained. Kubitzki (1938), on the other hand, used Prontosil without Fouadin,

employing injections of Prontosil Soluble and Prontosil Rubrum. Prompt fall of temperature and improvement of the local disease process resulted. It seems probable that Fouadin injections combined with an intensive 5—7 day treatment (2—3 g. daily) of Prontosil Rubrum merits trial in this disease.

Malaria

A. D. de Leon (1937) treated 15 cases of benign tertian malaria with a dye substance similar to Prontosil Rubrum and claimed success in each case. A report of a further 2 cases of malaria treated with Prontosil Album was published by van der Wielen (1937), and Hill and Goodwin (1937), who treated 100 patients in all, giving two injections of 10 c.c. Prontosil Soluble intramuscularly daily, found that four injections were sufficient to " give relief." No relapses occurred and two re-infections after 29 and 31 days respectively were cured by repetition of the same treatment. In contrast with the positive findings, recorded above, further work has shown that Prontosil can do little more than affect the temperature curve (and this only in tertian malaria), the parasite picture always remaining uninfluenced. (This unpromising clinical outlook bears out the negative results obtained in experimental work on bird malaria done in our laboratories in Elberfeld.)

Filariasis and Leprosy

Keil (1936) treated 13 lepers, 9 of whom had filariasis, with Prontosil ; change in neither the leprosy nor the number of filaria in the blood-stream was produced. In one patient, however, who suffered from acute attacks of lymphangitis and adenitis, due to streptococcal infection, which accompanied the exacerbations of filariasis, great improvement followed Prontosil treatment. Keil concluded that Prontosil might be of value in preventing elephantiasis. It is difficult, however, to believe that this will have any practical outcome.

Typhus

Prontosil has also been used in typhus fever by Kulesza, (1937) who reported 20 cures, 1 improvement and 5 uninfluenced in a series of 26 patients treated with injections of Prontosil. Again, the prospects seem doubtful.

THERAPEUTICS

THERAPEUTICS

Chapter IX.

ADMINISTRATION OF PRONTOSIL
(Including Dosage Schemes and Estimation in Body Fluids)

Prontosil, in one form or another, has been given orally, intramuscularly, intrathecally, intravenously, into the pleural cavity, and per rectum ; it has also been used as a local application. It may be shown in the future that oral and parenteral administration suffice for all cases, but the other methods mentioned in the literature are also described.

Prontosil Album

This is given orally, but it has also been used for local and parenteral administration. The solution, which has been mainly used in America, is prepared by crushing Prontosil Album tablets, mixing with water or saline, and then filtering the mixture ; the resulting solution, which contains 0.5—0.8 per cent. Prontosil Album, may be boiled. For local use Bosse (1938) recommended the following prescription :—

Prontosil Album	...	...	1.5
Alcohol (90 per cent.)	} āā	...	7.5
Acetone			
Glycerine ...	ad	...	100

This he used as a throat spray and also as a local application in cases of vaginal discharge. Prontosil Album ointment is made by crushing the tablets, suspending in water, filtering, and working into a 10 per cent. ointment with gelatine and glycerine. Lanoline or vaseline are also suitable bases.

*Prontosil Rubrum**

This is given orally, but it has been used in a saturated solution in equal quantities of alcohol and acetone for application to the skin.

*Prontosil Soluble**

It is important that this be given only by the intramuscular route, as intravenous injection is not without risk and appears

* *Prontosil Stains.* The azo-compounds may stain clothing. Stains may be removed by rinsing in water containing ʒii of sodium carbonate and ʒiii of sodium thiosulphate to the gallon.

to be no quicker in effect. Prontosil Soluble is also used, mixed with varying amounts of glycerine up to 20 per cent., as a paint for the mucous membrane, and it has been used alone as a paint and gargle.

Schemes of Dosage

In extremely severe infection the dosage should be high, and it is possible that it should be fixed according to the patient's body-weight. The Americans, Schwentker, Clason et alii gave 1 g. of sulphanilamide (Prontosil Album) per 20 lbs. body-weight with a maximum of 5 g. per day to patients suffering from streptococcal meningitis, and Prontosil Soluble was given in doses of ½ c.c. (5 per cent. solution) per pound of body-weight per day.

Standard Dosage

For practical purposes the following standard adult dosage should suffice. The children's dose is one-half, the infant's dose one-third, of what is given below.

Oral	Prontosil Album / Prontosil Rubrum	1—3 tablets (=0.5 to 1.5 g.) t.d.s.
Parenteral	Prontosil Soluble 5 per cent. solution	10—25* (or more) c.c. per 24 hrs. intra-muscularly.

Combined Treatment (P. Soluble and Album)

In most infections combined treatment (i.e. Prontosil Soluble *and* Prontosil Album) is recommended, except in urinary tract infections, erysipelas, mild conditions, and prophylaxis, where oral therapy alone suffices.

The dosage for combined treatment is as follows :—

Moderately Severe Case :—

Prontosil Soluble 10—15* c.c. per 24 hours.
plus Prontosil Album 1—2 tablets t.d.s.

Severe Case :—

Prontosil Soluble 20—25* c.c. per 24 hours.
plus Prontosil Album 1—2 tablets t.d.s.

Combined Treatment (P. Soluble and Rubrum)

For the benefit of those who wish to follow the scheme of combined treatment described by Colebrook (1936b) for cases

* These figures should be doubled if the original 2½ per cent. solution (obtainable if so specified) is used.

of puerperal infection, we give below the latter's dosage table. In this Prontosil Soluble ($2\frac{1}{2}$ per cent.) and Prontosil Rubrum (0.5 g. tablets) are used in combination.

Type of Case	*By mouth*	*By intramuscular injection* ($2\frac{1}{2}$ *per cent. solution*)
Gravely ill	8 tabs. per day (4 g.)	20 c.c. every 8 hours
Of moderate severity	4 tabs. per day	20 c.c. every 8 hours
Mild	4 tabs. per day	10—20 c.c. twice daily

Additional Points

So far as clinical experience has shown Prontosil Rubrum and Prontosil Album can be used with equally good results in similar doses. The choice at the moment must be left to individual practitioners, but the relative atoxicity of Prontosil Rubrum, and the possibility of a delayed excretion time, which might make this drug more suitable for prophylaxis in obstetrics and contaminated wounds, deserves further investigation.

The duration of treatment depends largely upon the nature of the case, but the drug should not be stopped as soon as clinical improvement has occurred. It is advisable to continue treatment for seven days, using a smaller dose, after the temperature has fallen to normal. A warning may be added to the effect that the use of any of the Prontosil compounds for prolonged periods (weeks or months) is not advised. If the clinical condition seems to demand continued therapy the patient should be kept under close observation and, where possible, intervals of rest should be interposed.

Whatever system of treatment is employed, no sulphur or sulphur containing compounds (viz., saline laxatives, such as Epsom and Glauber's salts, Mist. Alba, or Compound Liquorice Powder, Mist. Senna Co.) should be given. A suitable laxative is liquid paraffin. Avoidance of eggs and onions in the diet should also be observed. Mention of these and other precautions against the appearance of toxic effects will be found in Chapter X, which deals with this subject.

Estimation in Body Fluids

Until recently Prontosil has been given empirically, but it is possible that a dosage based on blood concentration may be adopted. Although Osgood (1938) claimed that sulphanilamide was effective under certain conditions in a concentration

of 1 : 100,000, no clinical trial with the small dosage required to achieve this concentration of Prontosil Album has been carried out, and many observers consider that the effective concentration in the blood lies between 1 : 5,000 and 1 : 10,000.

To attain and keep this concentration without estimating the sulphanilamide in the blood is a difficult matter, and Proom (1938) has recently published a method, given below, which is a combination of those suggested by Fuller, and Marshall et alii.

" One millilitre of blood, or body fluid, is diluted with 2 ml. of distilled water ; 1 ml. of a 20 per cent. aqueous solution of trichloracetic acid is then added, and the mixture filtered through a small filter-paper. To 1 ml. of the filtrate is added 0.05 ml. (1 drop of 0.5 per cent.) sodium nitrite solution. After 3 minutes 0.5 ml. of a 1 per cent. alcoholic solution of dimethyl α-naphthylamine is also added, and the whole mixed by gentle shaking. After standing for 15 minutes to allow the colour to reach its maximum intensity, the colour is compared with that obtained by treating in a similar manner standard solution containing known quantities of sulphanilamide. The comparison may be done in any of the usual forms of colorimeter."

A method of preparing permanent colour standards is mentioned, and it is claimed that it is possible to estimate the sulphanilamide to within 10 per cent.

Chapter X.

TOXIC EFFECTS OF PRONTOSIL

Some observers believe that the toxicity of all Prontosil preparations is very low, while others hold that the drugs are highly toxic. This difference of opinion is reflected in the literature, in that some reports mention a much higher incidence of toxic effects than others, a fact which may be accounted for by differences in the behaviour of the patients and in the assiduity with which such effects are sought.

As regards the relative toxicity of the three different forms of Prontosil animal experiments are not helpful, except in so far as they show discrepancies in different species and point to the pitfalls of drawing conclusions applicable to the human subject. Thus Kidwani (1938) showed that the mouse has a greater tolerability for sulphanilamide than for Prontosil Rubrum, the rat a slightly weaker tolerability, while in the rabbit the azo dye compounds were tolerated much better than was sulphanilamide. The feeling, freely expressed on the Continent, that the coloured Prontosils are less toxic than Prontosil Album, has not yet been strengthened by statistical proof; controlled clinical observations on this problem would, therefore, be of the greatest interest.

To return to generalities, however, it may be stated that while unpleasant after-effects of Prontosil treatment appear to be fairly common and extremely varied, the drug cannot be held to be highly toxic in the same way as quinine and digitalis, over-dosage of which is almost certain to be followed by symptoms of poisoning. With Prontosil, on the other hand, although increased dosage appears, according to Snodgrass and Anderson (1937), to cause a higher incidence of toxic effects (a belief which is not confirmed by other workers) reactions may occur in patients receiving the same dosage and living under the same conditions as others who remain unaffected. Many of the toxic effects, although unpleasant, are harmless, and some do not necessitate the cessation of treatment. They are dealt with serially below.

Cyanosis

Cyanosis following Prontosil treatment has been reported by a large number of observers in England and America, but it

appears to be uncommon on the Continent where the coloured drugs are more commonly used and the dosage is on the whole smaller. Three types of cyanosis have been described. In the first, mentioned by Cokkinis (1937), the patient's face, forehead, and neck were suffused with a rich pinkish colour; spectroscopic examination did not show any abnormality, a fact which was also noticed by Colebrook and Purdie (1937) who failed to detect abnormal absorption bands in the blood of eight cyanosed patients. The other two varieties are due to sulphæmoglobinæmia and methæmoglobinæmia, changes which usually occur separately, but which may both be present in one patient.

Nature of Met- and Sulphæmoglobinæmia

It cannot be said that the mechanism of either SHb or MHb is as yet fully explained. MHb is said to be due to oxidation of the iron-containing part of Hb, but how Prontosil brings this about is not clear, although Archer and Discombe (1937) concluded that any drugs containing C_6H_8N were capable of causing MHb. With regard to the formation of SHb, which is probably an addition product like COHb, experiments carried out at our Elberfeld laboratories suggested that the sulphur present in Prontosil was not responsible, while various observers pointed out that the sulphur in sulphates, eggs, and onions might play some part in causing this phenomenon.

This was investigated by Paton and Eaton (1937) who concluded that SHb probably arose from the administration of sulphates and Prontosil together, since the amino compounds had the property of catalysing the available H_2S to SHb. They also suggested that H_2S could not be excreted from the lungs. On the other hand, Archer and Discombe (1937), while believing that H_2S was normally excreted from the lungs, suggested that an excessive formation of H_2S (effected, for example, by purgation allowing unabsorbed foodstuffs to pass into the colon) or the presence of a suitable catalyst would cause the sulphide to combine with the Hb, resulting in the formation of SHb. In spite of these conclusions, however, and in spite of the fact that Prontosil-treated patients do not now receive sulphates, eggs, or onions, SHb and MHb still continue to appear.

In any case, whatever the ætiology of these manifestations, they present clinical differences which may assist the physician in determining which is present. In MHb the colour is blue tending to chocolate, while in SHb a lavender-blue tint may be seen. SHb is relatively persistent, taking a few days to clear up, whereas MHb disappears within a few hours of cessation of Prontosil treatment. In addition, the following spectroscopic method given by Colebrook and Purdie (1937) may be of value,

and it is interesting to note that spectroscopic examination may give positive results in cases in which cyanosis is not clinically detectable :

Detection of Met.- and Sulphæmoglobinæmia

" The oxalated blood was first laked by the addition of one volume of saponin solution, placed in a test tube of 3/8th inch diameter and examined with a direct-vision spectroscope. If a band in the red was observed, the blood was further diluted until this could be seen clearly, and its approximate wavelength determined. A band between 6150 and 6300 A.u. was taken to be due to sulphæmoglobin, and one between 6300 and 6400 as due to methæmoglobin. As a confirmatory test a drop of very dilute ammonium sulphide was added. The 6300-6400 band always disappeared while that between 6150 and 6300 always persisted, showing that these bands were due to met.- and sulphæmoglobin respectively. A rough indication of the amount of these substances present was made by finding the dilution at which these bands disappeared when viewed through the 3/8th inch tube. The sulphæmoglobin band was the more persistent, often being visible at a dilution of 1 in 30 to 1 in 50, while that of methæmoglobin rarely persisted above 1 in 10."

Treatment and Prophylaxis

Although the cyanosis is unpleasant, it appears to have no effect upon the action of the drug and little effect upon the patient's condition, as dyspnœa and cardiac embarrassment very seldom accompany this symptom. Occasionally, however, headache, constipation, and emotional instability may occur at the same time, and in cases of very severe anæmia the possibility of interference with the oxygen-carrying capacity of the blood should be borne in mind. There is no need to terminate treatment because of cyanosis unless it is extremely severe ; and although Frost (1937) reported a fatal case of a child who developed sulphæmoglobinæmia and died of respiratory failure, it is difficult to say what part SHb played in this case.

The prophylaxis of cyanosis is difficult in view of its unsettled ætiology, but it is wise to prohibit sulphates, eggs, and onions, and to prescribe a low residue diet for the patient. Purgatives causing a liquid motion are best avoided altogether ; liquid paraffin can be employed as a laxative, and phenacetin and coal tar drugs should not be given. If treatment is necessary in a severe case, the administration of oxygen may relieve MHb, while temporary improvement in SHb may be achieved by intravenous glucose-salines. In extremely severe cases blood transfusion may be required.

Agranulocytosis

The frequency of these cases and the extent to which the Prontosil group of drugs is responsible is difficult to assess. In proportion to the enormous number of patients treated with Prontosil, very few cases of agranulocytosis have been reported,

nor is it clear that the drugs mentioned were actually responsible for the condition. In one case, indeed, reported by Fitz-Hugh (1937), a patient suffering from agranulocytic angina with secondary hæmolytic streptococcal infection following amidopyrine treatment was cured by the administration of Prontosil Album ! A similar case was reported by Krauel (1937), and we have received further reports (unpublished) describing two more cases of agranulocytosis in which Prontosil was used in treatment. Bresgen (1937), after reporting a case of agranulocytosis following Prontosil treatment in which it appeared that the Prontosil was responsible for the condition, mentioned an almost exactly similar case occurring in a diabetic patient who had received nothing beyond injections of insulin. The author points out that had the second patient received a chemotherapeutic drug, or a barbiturate, the drug given would have been considered a likely cause for the agranulocytosis.

Reported Cases

So far as can be ascertained reports of 7 cases of agranulocytosis occurring during treatment with the Prontosil group of drugs have appeared in the literature.

The first case, reported by Borst (1937), was that of a woman of 61 who had suffered ten years before from thrombopenic purpura; because of pyelocystitis she received a total dosage of 79 g. of Prontosil Rubrum over a period of five weeks and died following the appearance of a rise of temperature, signs of pneumonia, difficulty in swallowing, and an almost complete disappearance of polymorphonuclear blood corpuscles.

In Young's (1937) case, a man of 63 received 54 g. of Prontosil Album in 18 days, after salicylates had failed to influence an attack of acute rheumatism. Four days after treatment was stopped complete agranulocytosis was observed and the patient died from septicæmia.

In the third fatal case, that of Model (1937), a patient suffering from acute rheumatism and, possibly, bacterial endocarditis was given 54 g. of benzyl-amino-benzene-sulphonamide in 18 days; two days later pharyngeal ulceration appeared, the leucocytes fell to 300 per c.mm. and death occurred despite pentnucleotide and blood transfusions.

A further case reported by Plumer (1937) concerned a female patient suffering from sub-acute bacterial endocarditis who died of agranulocytic angina after taking 47 g. Prontosil Album in, roughly, 6 weeks.

Schwartz et alii (1938) administered 56.6 g. of sulphanilamide to a 32-year-old man with a penile ulcer. Treatment was continued for 21 days, and suspended because of leukopenia; thereafter the patient became desperately ill and died of agranulocytic angina.

Berg et alii (1938) also reported a death from agranulocytic angina following the administration of 38 g. of sulphanilamide, which had been given in short courses with rest intervals.

Cases with Recovery

Although the prognosis in such cases is extremely bad, two cases of recovery are known.

In one (unpublished) a parturient woman received 60 g. Prontosil Album in 3 weeks; after the appearance of an acute anæmia and a fall in the polymorph count to 12 per cent., Prontosil was discontinued and Campolon and iron given.

The other recovered case was reported by Jennings and Southwell-Sander (1937); this occurred in a housewife who received 94.5 g. sulphanilamide in 3 weeks and developed angina of the pharynx on the third day of treatment. The white blood count fell to 2000 (2 per cent. polymorphs) and later to 444, but with pentnucleotide and Campolon treatment the patient recovered.

It is interesting to note that in the cases mentioned above the dosage was in all cases fairly high, and that treatment was carried out for from two to six weeks before the symptoms of agranulocytosis appeared. This is in marked contrast to the cases of acute hæmolytic anæmia dealt with in the next section, in which the symptoms appeared shortly after the drug was given.

Anæmia

Although the relationship between Prontosil and anæmia is not clear, it appears that two varieties of anæmia can occur during treatment with the sulphanilamide group of drugs, the first type, hæmolytic anæmia, being much the more serious. Three such cases were reported by Harvey and Janeway (1937) and Kohn (1937) reported a further case. In all four cases the anæmia appeared suddenly and shortly after treatment was begun, that is, on the 5th, 2nd, 7th, and 5th day respectively. The patients rapidly developed extreme pallor, the temperature rose, and blood counts showed a very marked fall in the red blood cells and hæmoglobin; in addition a varying degree of jaundice was detected. Leucocytosis was present, and in one case at least hæmoglobin appeared in the urine. All four patients recovered following blood transfusion, and two of Harvey and Janeway's patients were given a small dose of the drug after recovery with no change in the blood picture. Seven further cases of hæmolytic anæmia following sulphanilamide treatment were mentioned by Long and Bliss (1937b); no details of dosage are given. In this connection Singer (1938) reported an interesting case of hæmoglobinuria occurring in a male patient who had received 8 g. of Prontosil in four days; the hæmoglobinuria disappeared three days after treatment ceased.

The second type of anæmia was reported by Jennings and Southwell-Sander (1937), whose three patients developed a moderately severe hypochromic anæmia, without any signs of hæmolysis or icterus, after receiving fairly large doses of the drug (e.g. 36 and 152 g.). The temperature was not raised and the anæmia appeared some time after the cessation of treatment. All three patients recovered.

Acidosis

This was reported by Southworth (1937) who detected a fall in the CO_2-combining power of the plasma in patients with and without clinical acidosis. Long and Bliss (1937a) reported four cases of clinical acidosis which appeared to be associated with a loss of potassium and sodium in the urine, and these workers now give grs. 10 soda bic. with each dose of sulphanilamide. Basman et alii (1937) also noticed occasional cases of acidosis, and they recommended the administration of isotonic sodium *r*-lactate, 3—5 c.c. per kilo of body-weight in 24 hours, in such cases.

Disturbances of Vision

Visual disturbances have been recorded in a few cases, but optic neuritis has only been reported once—by Bucy (1937), who treated a girl of 16 suffering from chronic osteomyelitis with sulphanilamide. The drug was given in interrupted courses because of cyanosis and headache, and ultimately defective vision appeared ; on examination absolute scotomata for red and blue and relative central scotomata for white were discovered, and the discs were slightly swollen and reddened. The eyesight returned to normal in the course of the next month after treatment had been suspended.

Skin Eruptions and Drug Fever

Eruptions

The occurrence of rashes differing in nature and severity in patients treated with Prontosil Album and sulphanilamide has been frequently reported in this country and in America. Menville and Archinard (1937), and Goodman and Levy (1937) reported six cases in which the rashes were sudden in onset, itched severely, appeared only on parts exposed to sunlight (natural or artificial), and were red or dusky maculo-papular in character. In Menville and Archinard's cases the dosage was relatively high, and minute unerupted vesicles were noted, while one patient developed fever and leucocytosis ; slight cyanosis occurred in three cases.

A similar distribution of the eruption, corresponding to the exposed areas of the body, was described in four cases by Newman and Sharlit (1937). In two other cases Frank (1937) noticed that although the rash appeared in parts exposed to sunlight it quickly spread to unexposed portions of the body and that the rash was markedly œdematous in character, one patient showing vesiculation. A different rash occurred in a case noted by Schonberg (1937). The patient developed an urticarial eruption which covered the entire body and which, on fading,

left a purpuric eruption behind. Treatment resumed one month later was followed by the appearance of a scarlatiniform rash.

In the above cases the rashes disappeared fairly quickly after the cessation of treatment, but Myers et alii (1937) reported a case of exfoliative dermatitis following sulphanilamide treatment. The patient, a man of 25, received 88.3 g. sulphanilamide in 28 days. Afterwards he began to suffer from giddiness, weakness, and other systemic symptoms, and on the 28th day a rash spread over the whole body. The rash was maculopapular in character, bright red in colour, and purpuric in places. A week later the rash was exfoliative in character and a patch test gave a strongly positive result. He was discharged from hospital six weeks later with the skin condition still present on the feet and legs.

Drug Fever

This was mentioned by Colebrook et alii (1937 a and b). In 29.3 per cent. of the non-fatal cases the temperature, after falling to normal, rose sharply in 2 or 3 days, in several instances while the drug was being taken. The temperature rapidly subsided on ceasing administration of the drug. In other patients a rise of temperature several days after cessation of treatment, and attributable to a re-awakening of the infection, indicated the necessity for further treatment.

The next report was that of Hageman and Blake (1937), who described 21 cases in which a sudden rise of temperature occurred. The reaction appeared in most cases between the seventh and tenth day of sulphanilamide therapy, but in some instances the onset was as early as the fourth day or as late as the thirteenth. Nine patients developed maculopapular eruptions, occasionally accompanied by hæmorrhagic lesions and wheals. The distribution of these lesions was not on the exposed parts of the body only, but affected the buttocks, knees, and back as well. Cyanosis occurred in some cases and systemic reactions varied; malaise, nausea, itching, and tinnitus were noted as accompanying symptoms. The authors considered this an allergic phenomenon similar in character to serum sickness.

Other Toxic Effects

Agranulocytosis, acute anæmia, severe sulphæmoglobinæmia, and serious skin conditions occur much less frequently than the minor by-effects which include anorexia, nausea, vomiting, and diarrhœa, urinary irritation, headache, lassitude, dizziness and drowsiness, paræsthesiæ, and slight jaundice. Mental disturbance, tinnitus, slight degrees of deafness and loss of taste have also been mentioned.

Prevention and Treatment of Toxic Effects

A study of the above reports shows that the toxic effects of Prontosil and allied compounds present many unsolved problems. The relationship between the drug used and the effects produced is not clear, although it is suggestive that the bulk of the by-effects have been reported following the administration of the colourless compounds, and have occurred in countries where the red compounds are little used. Another question, that of the effect of the amount or length of administration, cannot as yet be answered, and the part played by idiosyncrasies in individual patients is no doubt important. A further possibility which may explain discrepancies in dosage is that some of the toxic effects are not due directly to the ingestion of too great an amount of Prontosil (as, for example, in strychnine poisoning) but are caused by an allergic or anaphylactic reaction to the drugs. It is plain that a great deal of investigation and correlation of results will be required before these difficulties are explained.

The prevention of toxic effects is a matter of some difficulty in view of the problems referred to above, but the following measures may be recommended.

(1) Reduce the dosage as soon as clinical progress permits.

(2) Avoid the administration of sulphates, eggs, and onions.

(3) If possible, continuous treatment should not be maintained for longer than two weeks.

(4) Do not expose patients to natural or artificial sunlight during treatment.

(5) Keep a careful watch for symptoms such as extreme pallor, sore throat, dyspnœa, and persistent vomiting.

(6) In severe infections it may be justifiable to continue treatment in the presence of cyanosis, drug fever, nausea, and slight jaundice, but only under strict observation.

(7) In severely ill patients, or those with a past history of anæmia or purpura, serial leucocyte counts should be done.

The treatment of the serious toxic effects has been dealt with above. As Prontosil, apart from the erratic effects reported, is not a consistently poisonous drug, no antidote (which has occasionally been asked for) exists, but excretion may be considerably hastened by forcing fluids. Thus, in a case described by Long and Bliss (1937a) a patient who took 12 g. of sulphanilamide in twelve hours developed headache, dizziness, nausea, and cyanosis ; thereafter within 6 hours she was given 5,000 c.c. of water by mouth, and after a few hours all signs of toxicity disappeared.

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